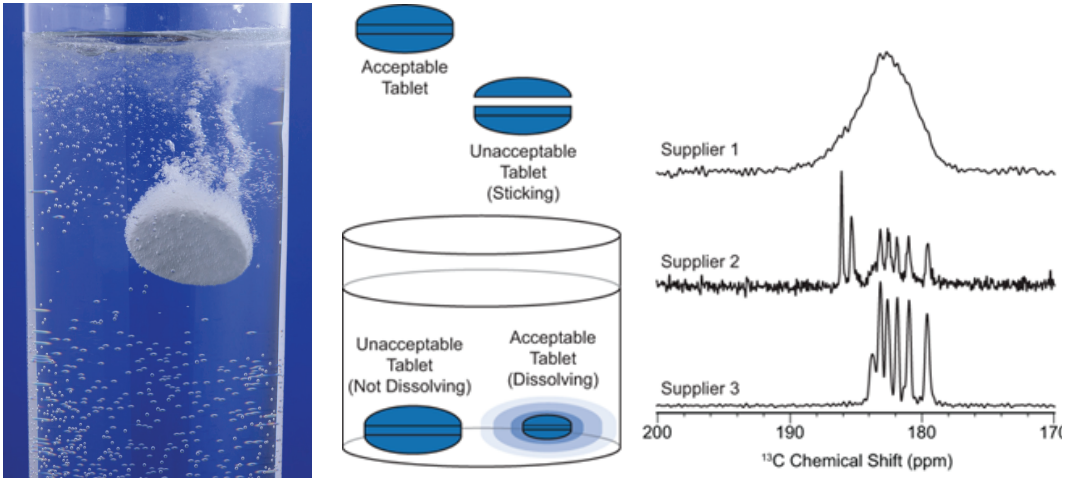
Center for Pharmaceutical Development (CPD)

Georgia Institute of Technology, Andy Bommarius, Director, 404.385.1334,
andreas.bommarius@chbe.gatech.edu
University of Kentucky, Eric Munson, 895.323.3107, eric.munson@uky.edu

Center website: http://cpd.gatech.edu

Improving Tablets Manufacturing

When reading the ingredients on the prescription bottles one will likely see magnesium stearate as one of the ingredients. The magnesium stearate is an inactive ingredient, or excipient, found in most solid tablets. It is typically found at relatively low levels (~1%) because it lubricates the stainless steel tablet forming machines used to process powders to form tablets. Without magnesium stearate, the powders that are compressed into tablets will build up and stick to the machines, leading to malformed tablets that cannot be sold and will result in significant loss of profits. This is a huge problem when hundreds of thousands of tablets per day are being produced.



A tablet remains intact when the proper amount of magnesium stearate is used in the tableting process (acceptable tablet). It breaks apart when too little magnesium stearate is used (unacceptable tablet). Center: Illustration of the tablets dissolving, where one is not dissolving because of too much magnesium stearate, and the other one is dissolving because it has the right amount of magnesium stearate. Right: Analytical data for three different suppliers of magnesium stearate, showing that the magnesium stearate is different from each supplier. Researchers are working to correlate the analytical data with tablets dissolving and breaking apart.

Even though magnesium stearate has been used for years in powder processing, failures are not well understood. Too much magnesium stearate can also result in soft tablets and slower dissolution. A confounding factor is that magnesium stearate from one supplier may behave differently from magnesium stearate from another supplier. This means that a manufacturing process may be fine one day and fail the next just because of the different batches of magnesium stearate.

Studying magnesium stearate, especially in a tablet, is difficult for several reasons. First, magnesium stearate is made from natural sources of stearic, palmitic, and other fatty acids. This means that it is a more complex material than the name implies. Commercially available magnesium stearate is a highly variable material and the differences in composition have significant impacts on the pharmaceutical manufacturing processes. This CPD work aims to understand how differences in composition affect the performance of the tablets.

CPD researchers have been using a powerful analytical technique to peek inside the tablets and determine how the active ingredient and excipients interact within a tablet. This technique, called solid-state nuclear magnetic resonance (NMR) spectroscopy, provides information about the chemical composition of the magnesium stearate, as well as about the changes that might have occurred when powder are processed. It even works on whole tablets that have not been broken.

Researchers are beginning to understand why one lot or supplier functions better than others. This is leading to improved understandings of how this excipient functions and will lead to the design of better pharmaceuticals and manufacturing processes.

> **Economic Impact**: Understanding how magnesium stearate functions in tablets will improve the manufacturing of both innovator drugs as well as generic tablets. In particular, CPD studies are helping to predict why some tablets fail to dissolve properly, which results in large scale batch losses and product recalls. Avoiding large-scale batch losses will result in lower cost of medicines and help keep a constant supply of both innovator and generic tablets on pharmacies' shelves.

For more information contact Eric Munson at the University of Kentucky, 859.323.3107, eric.munson@uky.edu.

Better/Cheaper Drugs: New Routes to Active Pharmaceutical Ingredients

More efficient manufacture of pharmaceuticals is helping drive down the cost of drugs to patients. It is also helping to keep high-end pharma industry manufacturing jobs in the United States.

Many active pharmaceutical ingredients, the part of a drug formulation responsible for its beneficial action, contain an amine group, similar to amino acids, the building blocks of life. Moreover, such amine groups have to be present as a single enantiomer and not a mixture. In other words, the amine groups have to have a very specific orientation in space, or else the drug most often either is ineffective or even detrimental (recall the case of Thalidomide, where the presence of the wrong enantiomer causes birth defects).

Pure amines are difficult to synthesize, so difficult in fact that the Pharmaceutical Roundtable of the American Chemical Society Green Chemistry Institute listed the generation of such pure amines from easily accessible ketone precursors as the second highest priority for novel, aspirational reactions. A team of CPD researchers has developed a novel protein biocatalyst that achieves just such a transformation to amines from ketones. They started from a known protein biocatalyst and engineered it to accept ketones and to synthesize the desired amines in great stereochemical purity.

Being able to catalyze the conversion from ketone substrates to amine products is such an important addition to the toolbox that it stands to develop into a platform technology, applicable to the synthesis of a wide variety of targets in several therapeutic areas. Production of active pharmaceutical ingredients via biological routes stands to increase yields and shorten process routes via enhanced selectivity of key steps. One CPD sponsor intends to make use of this new ability for its own drug synthesis development efforts. The pharmaceutical company will receive the first batch of protein in 2012, less than one year after the ultimately successful protein template was first begun for development. The company indicated that it has several potential targets to which it will apply this new technology.

Economic Impact: This technology could impact the synthesis of drugs that contain chiral centers adjacent to nitrogen by providing more efficient methods for their manufacture. Not only is this process considerably more economical than existing processes that use the traditional wholly chemical routes, but they also leave substantially reduced environmental footprints. The impact on the manufacture of a single blockbuster drug is can be in excess of a billion dollars over the lifetime of such a drug. In a comparable case, Merck recently published an improved route to the active ingredient of Januvia® and Janumet®, a drug soon to reach blockbuster status; that route is said to be at least 25% cheaper than the current one. In addition, such biologically-

inspired manufacturing with reduced environmental footprints are welcomed by most communities because processes to secure procure permits are greatly facilitated. In summary, more efficient manufacture of pharmaceuticals will help to drive down the cost of drugs to patients and help keep high-end pharma industry manufacturing jobs in the United States. As a result, this innovation can be expected to have broad economic impact across the pharmaceutical and fine chemical industries.

For more information, contact Andreas Bommarius, 404.385.1334, andreas.bommarius@chbe.gatech.edu.